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A Guiding Light for the Research Safe Harbor and “Research Tools”?

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Allele v. Pfizer – The Basics. On April 23, 2021 Pfizer, Inc., BioNTechSE, and BioNTech US, Inc. (“Pfizer and BioNTech”) filed a joint reply supporting of their previously filed motion to dismiss a patent infringement complaint filed by Allele Biotechnology and Pharmaceuticals, Inc. (“Allele”) in the Southern District of California. The patent at the center of the case is U.S. Pat. No. 10,221,221 (“the ’221 Patent”) which covers Allele’s mNeonGreen, a monomeric yellow-green fluorescent protein notable for its intense brightness. On May 4, 2021, the court denied the motion to dismiss, leaning heavily of the Federal Circuit’s 2008 decision *Proveris Science Corp. v. Innovasystems, Inc*. As this case continues to develop it could help shed light on an unsettled issue – are “research tools” categorically excluded from the 35 U.S.C. § 271(e)(1) Safe Harbor?

Allele has alleged that Pfizer and BioNTech infringed and continue to infringe the ’221 Patent through the use of a third party’s icSARS-CoV-2-mNG reporter virus that incorporates the mNeonGreen technology as a “research tool.” The reporter virus is used in a neutralization assay that allows the testing of patient sera for SARS-CoV-2 neutralizing antibodies and has been instrumental in determining the effectiveness of vaccines candidates, including BNT162b2. In response Pfizer and BioNTech moved to dismiss based on the affirmative defense of the research Safe Harbor.

The Safe Harbor. Section 271(e)(1) was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (“Hatch-Waxman Act”), in conjunction with patent term extensions (“PTE”) under § 156, to alleviate the distorting effects of patent terms and regulatory approval, to facilitate the approval of treatments, and undue the Federal Circuit’s decision in *Roche Products, Inc. v. Bolar Pharma. Co*. The Safe Harbor exempts otherwise infringing acts if they are done “solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.”

Since its enactment, the Safe Harbor has been interpreted and applied broadly, "extend[ing] to all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA." But, the Safe Harbor is still limited and does not apply to basic scientific research or routine testing. Whether the Safe Harbor applies is fact intensive and each use must be evaluated. While there is no per se rule barring the application of the Safe Harbor to post-approval activities, these activities are reviewed with heightened scrutiny.

Open Questions and Persisting Confusion. While the broad scope and general requirements of § 271(e)(1) are established, whether "research tools" are exempt is not a bright line rule. In Merck, the Supreme Court punted on the question. Without a definitive answer from the Supreme Court and divergent Federal Circuit cases, district courts have varied in their application of the Safe Harbor creating uncertainty as to whether "research tools" are eligible. This confusion persists because it's not clear whether a patent must be eligible for PTE for the Safe Harbor to be available.

In *Eli Lilly & Co. v. Medtronic, Inc.*, the Supreme Court affirmed the Federal Circuit and held that the § 271(e)(1) Safe Harbor was available for a defibrillator, a class III device subject to premarket approval. This decision found that devices were encompassed within term "patented inventions" of § 271(e)(1) based on the overall statutory scheme. Later, in *Abtox Inc. v. Exitron Corp.*, the Federal Circuit held that the Safe Harbor applied to a medical instrument sterilization device, a class II device not subject to full regulatory review. While the court recognized that under a narrow reading of Eli Lilly there should be symmetry between §§ 271(e)(1) and 156, it applied the broader ruling that all medical devices were within the scope of the Safe Harbor, irrespective of eligibility for PTE. The court noted that "the Supreme Court commands that statutory symmetry is preferred but not required."

Following the Supreme Court's decision in Merck, the Federal Circuit shifted direction in *Proveris Scientific Corp. v. Innovasystems, Inc*. There the issue was whether the manufacture and sale of a spray data acquisition system, again a class II device, was exempt under the Safe Harbor. The system manufacturer sold the device to others who would use it to generate data that was then submit to the FDA. The Proveris panel applied the narrower holding of Eli Lilly—requiring statutory symmetry—and held that the spray data acquisition system was not protected by the Safe Harbor since the system was not subject to FDA approval and the manufacturer did not suffer the distorting effects of patent term and regulatory review. Following these cases some district courts have required that a patent be eligible for PTE for the Safe Harbor to be available while others have not.

Allele v. Pfizer may be an opportunity to clarify the application of the Safe Harbor to "research tools". In denying the MTD, the court found Proveris controlling that that Pfizer and BioNTech did not establish that the mNeonGreen is a "patented invention" for the application of the § 271(e)(1) Safe Harbor. Under this application there must be symmetry between §§ 271(e)(1) and 156. Since "research tools" are not subject to FDA regulation this would effectively treat an entire class of patents as ineligible for the protection of the Safe Harbor.

Still, this does not definitively establish the contours of the Safe Harbor and it is not likely the last we see this issue litigated in this case. Additionally, the same defense has already been raised in Allele's related case against Regeneron Pharmaceuticals Inc. It's worth noting that *Allele v. Regeneron* is in the Southern District of New York were a previous court distinguished Proveris, did not require statutory symmetry, and permitted the application of the Safe Harbor to peptide markers used for calibrating columns. Unfortunately, the limits of the Safe Harbor will likely stay unresolved until the higher courts clarify that "research tools" are categorically excluded or the "reasonably related" test applies to all uses of inventions.

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